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(54) **NOVEL INTERMEDIATES FOR THE PREPARATION OF ANTIHISTAMINIC 4-DIPHENYLMETHYL/DIPHENYLMETHOXY PIPERIDINE DERIVATIVES**

NEUE ZWISCHENPRODUKTE FÜR DIE HERSTELLUNG VON ANTIHISTAMINSCHEN 4-DIPHENYLMETHYL/DIPHENYLMETHOXYPIPERIDIN-DERIVATEN

NOUVEAUX INTERMEDIAIRES UTILISES DANS LA PREPARATION DE DERIVES DE PIPERIDINE 4-DIPHENYLMETHYL/DIPHENYLMETHOXY ANTIHISTAMINIQUES

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Remarks:

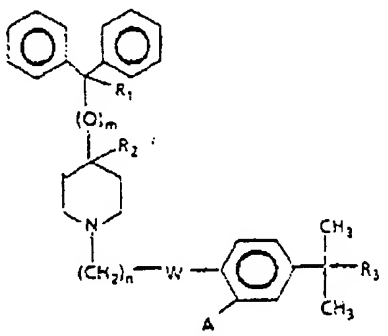
The file contains technical information submitted after the application was filed and not included in this specification

Description

BACKGROUND OF THE INVENTION

[0001] The present invention is related to novel intermediates which are useful in the preparation of certain piperidine derivatives which are useful as antihistamines, antiallergy agents and bronchodilators US-A-4,254,129 (March 3, 1981), US-A-4,254,130 (March 3, 1981), US-A-4,285,958 (April 25, 1981) and US-A-4,550,116 (Oct. 29, 1985).

[0002] These antihistaminic piperidine derivatives can be described by the following formula:



(I)

wherein

W represents -C(=O)- cr -CH(OH)-;

R_1 represents hydrogen or hydroxy;

R_2 represents hydrogen;

R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2;

n is an integer of from 1 to 5;

m is an integer 0 or 1;

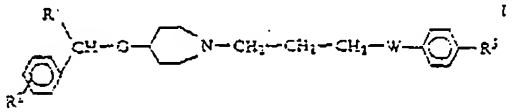
R_3 is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;

each of A is hydrogen or hydroxy; and

pharmaceutically acceptable salts and individual optical isomers thereof,

with the proviso that where R_1 and R_2 are taken together to form a second bond between the carbon atoms bearing R_1 and R_2 or where R_1 represented hydroxy, m is an integer 0.

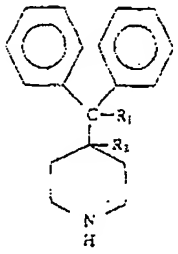
[0003] US-A- 4,550,116 discloses compounds of the general formula



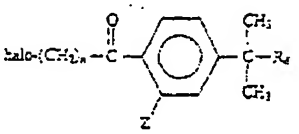
(I)

and pharmaceutically acceptable salts thereof which are prepared by condensation of α-substituted benzylhalides with N-(benzoylpropyl or phenyl-hydroxypropyl)-4-hydroxy piperidines or condensation of di-substituted-methoxy-piperidines with a benzoylpropyl halide or a phenyl-hydroxypropylhalide.

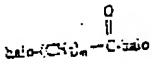
[0004] In US-A-4,254,129, 4,254,130 and 4,285,958 4-[4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α-α-dimethylbenzeneacetic acid and related compounds are prepared by alkylation of a substituted piperidine derivative of the formula



with a ω-haloalkyl substituted phenylketone of the formula



wherein the substituents halo, R_1, R_2, n, Z and R_6 are described in column 6 of US Patent 4,254,130.
It is further described that the ω-haloalkyl substituted phenyl ketones wherein Z is hydrogen are prepared by reacting an appropriate straight or branched lower alkyl C_1-C_6 ester of α,α-dimethylphenylacetic acid with the compound of the following formula:



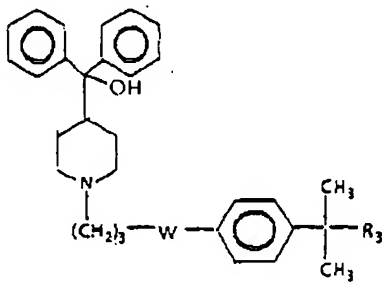
under the general conditions of a Friedl-Craft's acylation, wherein halo and m are described in column 11 of US-A-4,254,129.

[0005] Rovnyak G. et al describe the synthesis and antiinflammatory activities of (α-cyclopropyl-p-tolyl)acetic acid and related compounds. in Journal of Medical Chemistry, vol.16, no.15, 1973, pp. 487-490.

[0006] In Sulfur Letters, vol. 15, no.3, 1993, pp. 127-133 Roche D. et al. disclose the synthesis of cyclopropylvinylsulfones by Peterson Olefination.

SUMMARY OF THE INVENTION

[0007] The present invention provides novel intermediates useful for the preparation of certain antihistaminic piperidine derivatives of formula (I')



(I')

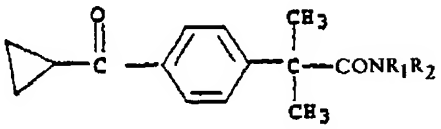
wherein

W represents -C(=O)- or -CH(OH)-;

R_3 is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
each of A is hydrogen or hydroxy; and
pharmaceutically acceptable salts and individual optical isomers thereof.

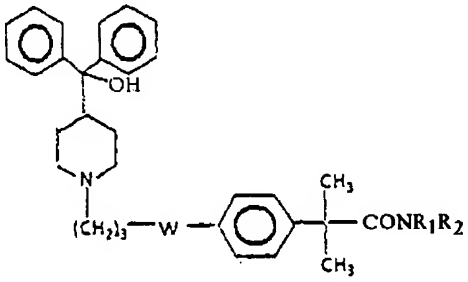
[0008] The novel intermediates are described by the following formulae:

(III)



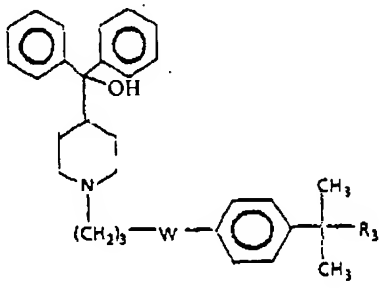
wherein R_1 represents C_1-C_6 alkyl and
R_2 represent H, C_1-C_6alkyl, C_1-C_6alkoxy or R_1 and R_2 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine.

(XI)



wherein
W represents -C(=O)- or -CH(OH)-;
R_1 represents C_1-C_6 alkyl
and R_2 represents H, C_1-C_6alkyl, C_1-C_6alkoxy or R_1 and R_2 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine.

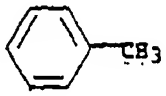
[0009] Another embodiment of the present invention involves a process for preparing the piperidine derivatives of formula



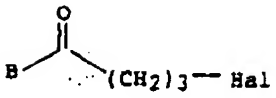
(I')

wherein
W represents -C(=O)- or -CH(OH)-;
R_3 is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched;
each of A is hydrogen or hydroxy; and
pharmaceutically acceptable salts and individual optical isomers thereof, comprising the steps of:

(a) reacting a toluene compound of the formula



with a ω-halo compound of the formula



wherein B is halo or hydroxy, Hal represents Cl, Br or I and n is as defined above, in the presence of a suitable Lewis acid to produce a ω-halo-tolylketone compound;

(b) reacting the ω-halo-tolylketone compound with a suitable base to give a cyclopropyl-tolylketone compound;

(c) reacting the cyclopropyl-tolylketone compound with a suitable halogenating agent to give a cyclopropyl-halo-tolylketone compound;

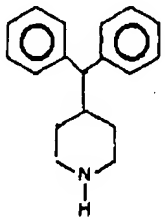
(d) reacting the cyclopropyl-halotolylketone compound with a suitable cyanating agent to give a cyclopropyl cyanotolylketone compound;

(e) reacting the cyclopropyl cyanotolylketone compound with a suitable methylating agent to give a cyclopropyl cyanocumylketone compound;

(f) reacting the cyclopropyl cyanocumylketone compound with a suitable base to give a cyclopropylketo-α,α-dimethylphenylacetic acid amide;

(g) reacting the cyclopropylketo-α,α-dimethylphenylacetic acid amide with an appropriate straight or branched C_1-C_6 alcohol in the presence of a suitable anhydrous acid to give a ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound;

(h) reacting the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound with a piperidine compound of the formula



wherein R_1, R_2 and m are as defined above in the presence of a suitable non-nucleophilic base to produce a ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative;

(i) optionally hydrolyzing the ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative to produce a ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is COON and W is -C(=O)-;

(j) optionally reacting the ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is COOH and W is -C(=O)- with a suitable reducing agent to produce a ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)-; and

(k) optionally reacting the ω'-piperidine-a'-hydroxy-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the appropriate ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (I) wherein R^3 is -COOH and W is -C(=O)- with an appropriate straight or branched C_1-C_6 alcohol in the presence of a suitable acid to produce a ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is -COOalkyl and W is CH(OH)- or a ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (II) wherein R_3 is -COOalkyl and W is -C(=O)-; and

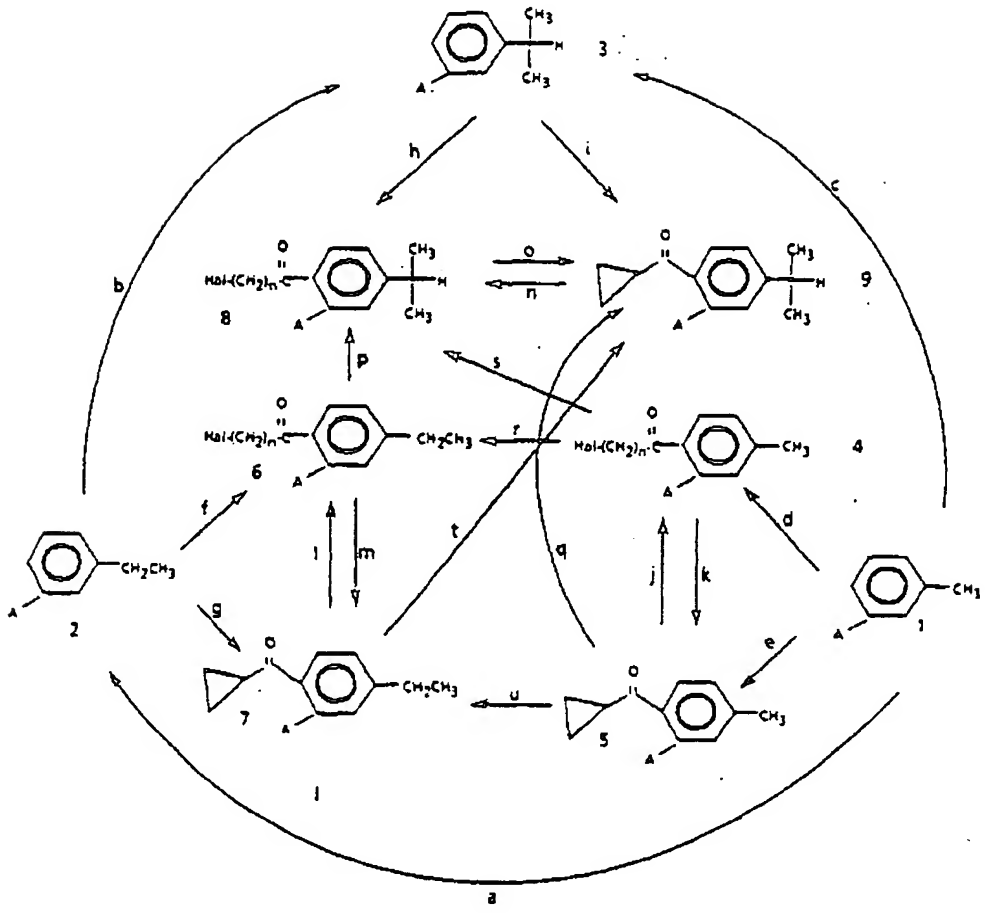
(l) optionally reacting the ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (II) wherein R_3 is -COOH and W is -C(=O)-, the ω'-piperidine-α'-keto-α,α-dimethylphenyl derivative of formula (II) wherein R_3 is -COOalkyl and W is -C(=O)-, the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl derivative of formula (I) wherein R_3 is -COOH and W is -CH(OH)- or the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl of formula (I) wherein R_3 is -COOalkyl and W is -CH(OH)- with an appropriate deprotecting reagent,

with the proviso that each of the hydroxy groups present in the compounds described in steps a-k are optionally protected or unprotected.

[0010] As used herein, the term "C_1-C_6alkyl" or "alkyl" refers to a straight or branched alkyl group having from 1 to 6 carbon atoms and as referred to herein are methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, neopentyl and n-hexyl. The term "C_1-C_6alkoxy" refers to a straight or branched alkoxy group having from 1 to 6 carbon atoms and as referred to herein are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, neopentoxy and n-hexoxy. The term "Hal" or "halo" refers to a halogen group and includes Cl, Br or I.

[0011] The piperidine derivatives of the formula (XI) can form pharmaceutically acceptable salts. Pharmaceutically acceptable acid addition salts of the compounds of this invention are those of any suitable inorganic or organic acid. Suitable inorganic acids are, for example, hydrochloric, hydrobromic, sulfuric, and phosphoric acids. Suitable organic acids include carboxylic acids, such as, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, malic, tartaric, citric, cyclamic, ascorbic, maleic, hydroxymaleic, and dihydroxymaleic, benzoic, phenylacetic, 4-aminobenzoic, 4-hydroxybenzoic, anthranillic, cinnamic, salicyclic, 4-aminosalicyclic, 2-phenoxybenzoic, 2-acetoxybenzoic, and mandelic acid, sulfonic acids, such as, methanesulfonic, ethanesulfonic and β-hydroxyethanesulfonic acid. Non-toxic salts of the compounds of the above-identified formula formed with inorganic or organic bases are also included within the scope of this invention and include, for example, those of alkali metals, such as, sodium, potassium and lithium, alkaline earth metals, for example, calcium and magnesium, light metals of group IIIA, for example, aluminum, organic amines, such as, primary, secondary or tertiary amines, for example, cyclohexylamine, ethylamine, pyridine, methylaminoethanol and piperazine. The salts are prepared by conventional means as, for example, by treating a piperidine derivative of formula (I) with an appropriate acid or base.

Reference - Scheme A



[0012] Reference - Scheme A provides various general synthetic procedures for preparing intermediates not covered by the present invention.

[0013] In step a, the appropriate toluene derivative of structure (1) is methylated to give the corresponding ethylbenzene derivative of structure (2).

[0014] For example, toluene of structure (1) is reacted with a slight molar excess of an appropriate methylating agent, such as iodomethane, chloromethane or bromomethane in the presence of a suitable non-nucleophilic base, such as potassium t-butoxide or sodium hydride. The reaction is typically conducted in a suitable organic solvent, such as diglyme, tert-butyl methyl ether or methylene chloride, for a period of time ranging from 30 minutes to 24 hours and at a temperature range of from -78°C to room temperature. The corresponding ethylbenzene derivative of structure (2) is recovered from the reaction zone by extractive methods as is known in the art and may be purified by distillation.

[0015] In step b, the appropriate ethylbenzene derivative of structure (2) is methylated to give the corresponding cumene derivative of structure (3) as described previously in step a, but using at least 2 molar equivalents of methylating agent.

[0016] In step c, the appropriate toluene derivative of structure (1) is dimethylated to give the corresponding cumeme derivative of structure (3) as described previously in step a but using at least 2 molar equivalents of methylating agent.

[0017] In step d, the appropriate toluene derivative of structure (1) is acylated with an appropriate ω-halo compound

of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω-halo tolylketone compound of structure (4).

[0018] For example, the appropriate ω-halo tolylketone compound of structure (4) may be prepared by reacting an appropriate toluene derivative of structure (1) with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined, which are known in the art or are prepared by procedures well known in the art, under the general conditions of a Friedel-Crafts acylation using a suitable Lewis acid. The reaction is carried out in a solvent, such as carbon disulfide, 1,2-dichloroethane, n-hexane, acetonitrile, 1-nitropropane, nitromethane, diethyl ether and carbon tetrachloride, methylene chloride, tetrachloroethane or nitrobenzene with methylene chloride being the preferred solvent. The reaction time varies from about 1/2 hour to 25 hours, preferably 10 to 16 hours and the reaction temperature varies from about 0°C to 25°C. The corresponding ω-halo tolylketone compound of structure (4) is recovered from the reaction zone by an aqueous quench followed by extraction as is known in the art. The ω-halo tolylketone compound of structure (4) may be purified by procedures well known in the art, such as crystallization and/or distillation.

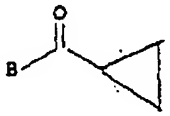
[0019] Alternatively, the appropriate toluene derivative of structure (1) may be acylated with the ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is hydroxy, Hal is Cl, Br or I and n is as previously defined in the presence of a Lewis acid to give the corresponding ω-halo tolylketone compound of structure (4) as described in *Arch. Pharm.* 306, 807 **1973.** In general, an appropriate toluene derivative of structure (1) and the ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is hydroxy, are melted together at about 50°C, then cooled to about 10°C after which a Lewis acid is added in an amount about 2.2 times the molar amount of the appropriate toluene derivative of structure (1) employed. The mixture is heated at about 70°C for about 2 hours after which a 30% sodium acetate solution is added and extracted with ether. The organic layer is dried and the solvent evaporated to give the corresponding ω-halo tolylketone compound of structure (4). The ω-halo tolylketone compound of structure (4) may be purified by procedures well known in the art, such as crystallization and/or distillation.

[0020] Suitable Lewis acids for the acylation reaction described in step d are well known and appreciated in the art. Examples of suitable Lewis acids are boron trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride, ferric chloride, cobalt(II) chloride and zinc chloride, with aluminum chloride being preferred. The selection and utilization of suitable Lewis acids for the acylation reaction of step d is well known and appreciated by one of ordinary skill in the art.

[0021] The starting ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined are commercially available easily prepared by generally known methods.

[0022] While also not necessary for utilization in the acylation reaction of step d, the phenol functionality of those toluene derivatives of structure (1), wherein A is hydroxy may be protected with a suitable protecting group. For example, suitable protecting groups for the phenolic hydroxy include methyl ether, 2-methoxyethoxymethyl ether (MEM), cyclohexyl ether, o-nitrobenzyl ether, 9-anthryl ether, t-butyldimethylsilyl ether, acetate, benzoate, methyl carbamate, benzyl carbamate, aryl pivaloate and aryl methanesulfonate.

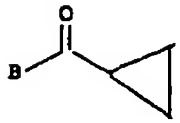
[0023] In step e, the appropriate toluene derivative of structure (1) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropyl tolylketone derivative of structure (5) as described previously in step d.

[0024] In step f, the appropriate ethylbenzene derivative of structure (2) is acylated with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω-halo ethylphenylketone compound of structure (6) as described previously in step d.

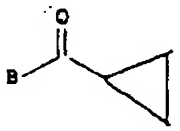
[0025] In step g, the appropriate ethylbenzene derivative of structure (2) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step e.

[0026] In step h, the appropriate cumene derivative of structure (3) is acylated with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω-halo cumylketone compound of structure (8) as described previously in step d.

[0027] In step i, the appropriate cumene derivative of structure (3) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step e.

[0028] In step j, the cyclopropyl functionality of the appropriate cyclopropyl tolylketone derivative of structure (5) is ring-opened to give the corresponding ω-halo tolylketone compound of structure (4) wherein n = 3.

[0029] For example, the appropriate cyclopropyl tolylketone derivative of structure (5) is reacted with an appropriate hydrogen halide in a suitable organic solvent, such as toluene, xylene and ethanol. The reaction is typically conducted at a temperature range of from room temperature to 70°C and for a period of time ranging from 20 minutes to 10 hours. The corresponding ω-halo tolylketone compound of structure (4) wherein n = 3 is isolated from the reaction zone by evaporation of the solvent or may be stored in a solution of the hydrogen halide.

[0030] In step k, the appropriate ω-halo tolylketone compound of structure (4) wherein n = 3 is ring-closed to give the corresponding cyclopropyl tolylketone derivative of structure (5).

[0031] For example, the appropriate ω-halo tolylketone compound of structure (4) wherein n = 3 is reacted with an appropriate non-nucleophilic base, such as sodium hydroxide or potassium hydroxide in a suitable organic protic solvent, such as methanol or ethanol. The reaction is typically conducted at a temperature range of from -10°C to room temperature and for a period of time ranging from 10 minutes to 5 hours. The corresponding cyclopropyl tolylketone derivative of structure (5) is isolated from the reaction zone by extractive methods as are known in the art and may be purified by distillation.

[0032] In step l, the cyclopropyl functionality of the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is ring-opened to give the corresponding ω-halo ethylphenylketone compound of structure (6) wherein n = 3 as described previously in step j.

[0033] In step m, the appropriate ω-halo ethylphenylketone compound of structure (6) wherein n = 3 is ring-closed to give the corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step k.

[0034] In step n, the cyclopropyl functionality of the appropriate cyclopropyl cumylketone derivative of structure (9) is ring-opened to give the corresponding ω-halo cumylketone compound of structure (8) wherein n = 3 as described previously in step j.

[0035] In step o, the appropriate ω-halo cumylketone compound of structure (8) wherein n = 3 is ring-closed to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step k.

[0036] In step p, the appropriate ω-halo ethylphenylketone compound of structure (6) is methylated to give the corresponding ω-halo cumylketone compound of structure (8) as described previously in step a.

[0037] In step q, the appropriate cyclopropyl tolylketone derivative of structure (5) is dimethylated to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step c.

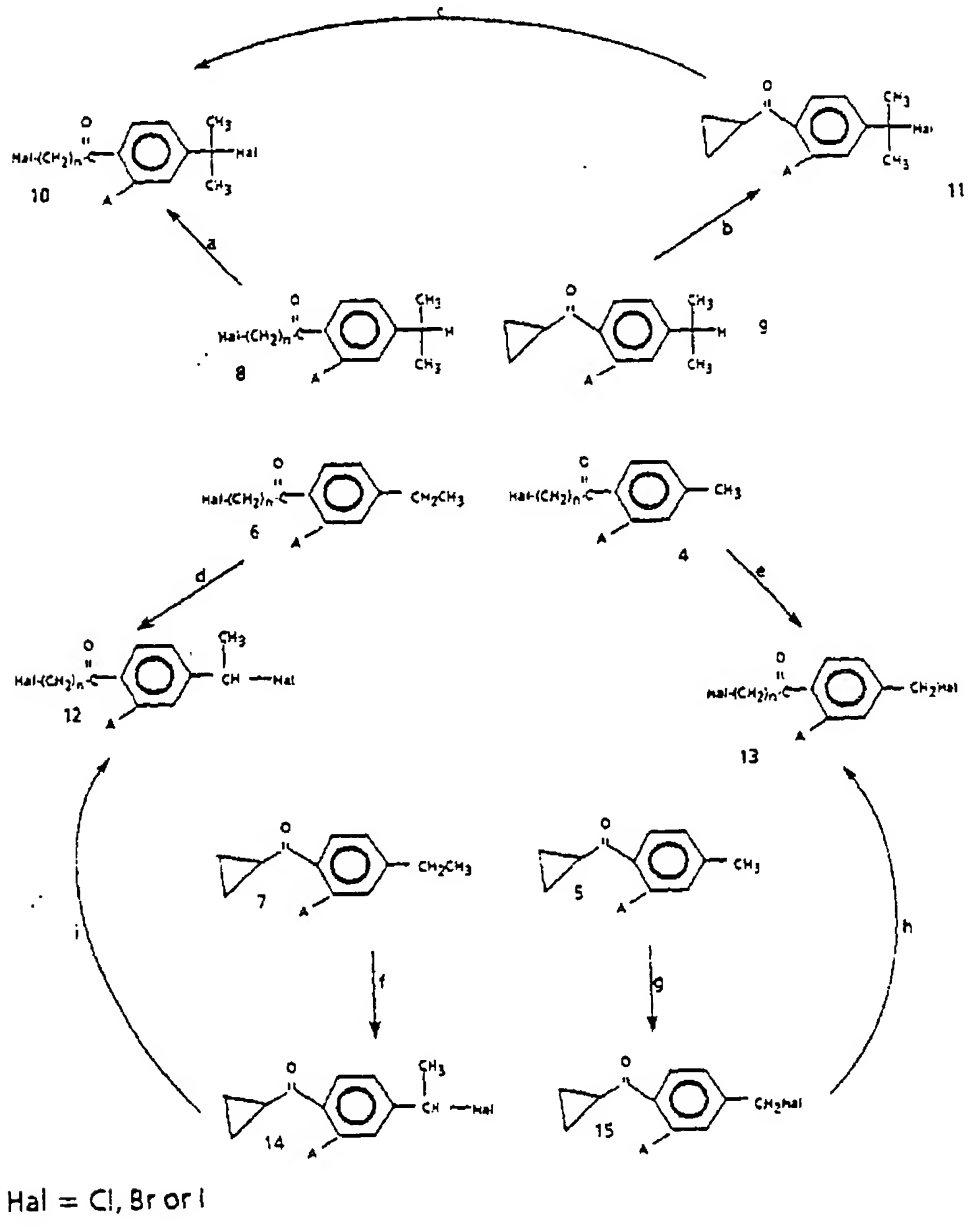
[0038] In step r, the appropriate ω-halo tolylketone compound of structure (4) is methylated to give the corresponding ω-halo ethylphenylketone compound of structure (6) as described previously in step a.

[0039] In step s, the appropriate ω-halo tolylketone compound of structure (4) is dimethylated to give the corresponding ω-halo cumylketone compound of structure (8) as described previously in step c.

[0040] In step t, the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is methylated to give the corresponding cyclopropyl cumylketone derivative of structure (9) as described previously in step a.

[0041] In step u, the appropriate cyclopropyl tolylketone derivative of structure (5) is methylated to give the corresponding cyclopropyl ethylphenylketone derivative of structure (7) as described previously in step a.

Reference-Scheme B



[0042] Reference - Scheme B provides various general synthetic procedures for preparing intermediates not covered by the present Invention.

[0043] In step a, the appropriate ω-halo cumylketone compound of structure (8) is halogenated to give the corresponding ω-halo-halocumylketone compound of structure (10).

[0044] For example, the appropriate ω-halo-halocumylketone compound of structure (10) may be prepared by reacting an appropriate ω-halo cumylketone compound of structure (8) with a suitable halogenating agent optionally in the presence of a catalytic amount of a suitable initiator. Examples of suitable brominating agents are N-bromosuccinimide, and 1,3-dibromo-5,5-dimethyl hydantoin, with N-bromosuccinimide being preferred. An example of suitable chlorinating agent is N-chlorosuccinimide and an example of a suitable iodinating agent is N-iodosuccinimide. Examples of suitable initiators are benzoyl peroxide, AIBN, t-butyl peroxide and ultraviolet light. The reaction is carried out in a solvent, such as carbon tetrachloride, methylene chloride, 1,2-dichlorobenzene, 1,2-dichloroethane, ethyl formate or ethyl acetate, with carbon tetrachloride being the preferred solvent. The reaction time varies from about 1/2 hour to 8 hours, preferably 1/2 to 2 hours and the reaction temperature varies from about 25°C to the reflux temperature of the solvent employed, preferably 70°C to 80°C. The corresponding ω-halo-halocumylketone compound of structure (10) is recovered from the reaction zone by extractive methods as are known in the art followed by evaporation of the solvent.

[0045] In addition, the halogenation reaction of step a may be carried out in a 2-phase procedure. For example, the appropriate ω-halo-halocumylketone compound of structure (10) may be prepared by reacting an appropriate ω-halo cumylketone compound of structure (8) with a suitable halogenating agent, such as sodium bromate/sodium bromide, in a solvent mixture such as methylene chloride and water, catalyzing the reaction with, for example, ultraviolet light. The corresponding ω-halo-halocumylketone compound of structure (10) is recovered from the reaction zone by extractive methods as are known in the art followed by evaporation of the solvent.

[0046] The ω-halo-halocumylketone compound of structure (10) may dehydrohalogenate to the corresponding α-methylstyrene, giving various mixtures of ω-halo-halocumylketone compound of structure (10) and α-methylstyrene compounds. The α-methylstyrene compounds in such a mixture may be back-converted to ω-halo-halocumylketone compound of structure (10) by treatment with anhydrous hydrogen halide gas. Typically, a solution of the mixture of ω-halo-halocumylketone compound of structure (10) and α-methylstyrene compounds in a suitable organic solvent, such as methylene chloride or acetonitrile, is treated with a suitable anhydrous hydrogen halide gas, such as hydrogen chloride. The reaction is typically treated with the hydrogen halide gas for a period of time ranging from 30 minutes to 5 hours and at a temperature range of from 0°C to room temperature. The remedied ω-halo-halocumylketone compound of structure (10) may be isolated by evaporation of solvent, but may be stored as a solution in the organic solvent containing hydrogen halide gas.

[0047] In addition, halogen exchange of the benzylic halogen can be accomplished by thorough solvolysis in the presence of the appropriate hydrogen halide.

[0048] For example, the ω-chloro-halocumylketone compound of structure (10) can be prepared from the ω-bromo-halocumylketone compound of structure (10) by thorough aqueous solvolysis in the presence of hydrogen chloride.

[0049] In step b, the appropriate cyclopropyl cumylketone derivative of structure (9) is halogenated to give the corresponding cyclopropyl halocumylketone compound of structure (11) as described previously in step a.

[0050] In step c, the cyclopropyl functionality of the appropriate cyclopropyl halocumylketone compound of structure (11) is ring-opened to give the corresponding ω-halo-halocumylketone compound of structure (10) wherein n = 3 as described previously in Scheme A, step j.

[0051] In step d, the appropriate ω-halo ethylphenylketone compound of structure (6) is halogenated to give the corresponding ω-halo-haloethylphenylketone compound of structure (12) as described previously in step a.

[0052] In step e, the appropriate ω-halo tolylketone compound of structure (4) is halogenated to give the corresponding ω-halo halotolylketone compound of structure (13) as described previously in step a.

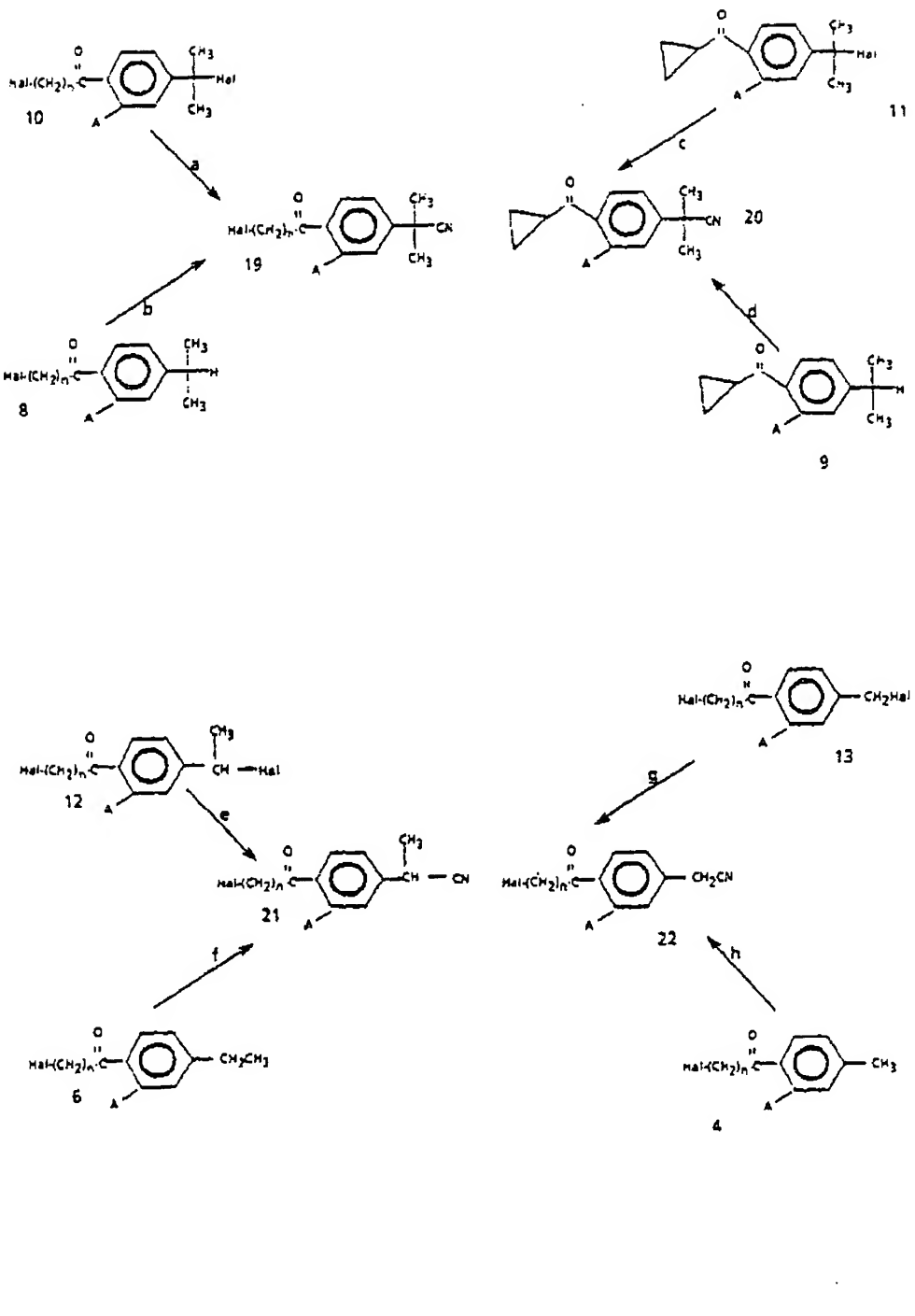
[0053] In step f, the appropriate cyclopropyl ethylphenylketone derivative of structure (7) is halogenated to give the corresponding cyclopropyl haloethylphenylketone compound of structure (14) as described previously in step a.

[0054] In step g, the appropriate cyclopropyl tolylketone derivative of structure (5) is halogenated to give the corresponding cyclopropyl halotolylketone of structure (15) as described previously in step a.

[0055] In step h, the appropriate cyclopropyl halotolylketone of structure (15) is ring-opened to give the corresponding ω-halo halotolylketone compound of structure (13) wherein n = 3 as described previously in Scheme A, step j.

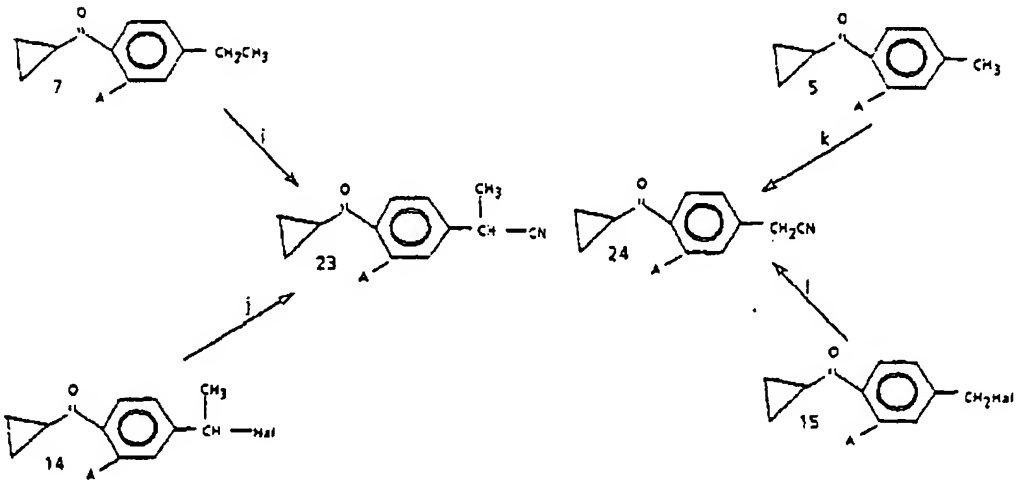
[0056] In step i, the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is ring-opened to give the corresponding ω-halo-haloethylphenylketone compound of structure (12) wherein n = 3 as described previously in Reference-Scheme A, step j.

Reference-Scheme D



[0057] Reference -Scheme D provides various general synthetic procedures for preparing intermediates,

Reference - Scheme D Cont.



not covered by the present invention.

[0058] In step a, the appropriate ω-halo-halocumylketone compound of structure (10) is cyanated to give the corresponding ω-halo-cyanocumylketone compound of structure (19).

[0059] For example, the appropriate ω-halo-cyanocumylketone compound of structure (19) may be prepared by reacting an appropriate ω-halo-halocumylketone compound of structure (10) with a suitable cyanating agent. Examples of suitable cyanating agents are trimethylsilyl cyanide, diethylaluminum cyanide and tetrabutylammonium cyanide, with trimethylsilyl cyanide being preferred. The reaction is carried out in a solvent, such as methylene chloride, tetrachloroethane and carbon tetrachloride, with methylene chloride being the preferred solvent. A catalytic amount of a suitable Lewis acid may also be employed in the reaction. Examples of suitable Lewis acids are boron trichloride, aluminum chloride, titanium tetrachloride, boron trifluoride, tin tetrachloride and zinc chloride, with tin tetrachloride being preferred. The reaction time varies from about 1/2 hour to 8 hours, preferably 1/2 to 2 hours and the reaction temperature varies from about 0°C to room temperature, preferably room temperature. The ω-halo-cyanocumylketone compound of structure (16) is recovered from the reaction zone by an aqueous quench followed by extraction as is known in the art. The ω-halo-cyanocumylketone compound of structure (16) may be purified by procedures well known in the art, such as chromatography and crystallization.

[0060] In step b, the appropriate ω-halo cumylketone compound of structure (8) is cyanated to give the corresponding ω-halo-cyanocumylketone compound of structure (19).

[0061] For example, the ω-halo-cyanocumylketone compound of structure (19) may be prepared by reacting an appropriate ω-halo cumylketone compound of structure (8) with a suitable cyanating agent. Examples of suitable cyanating agent are cyanogen chloride, cyanogen bromide and cyanogen iodide, with cyanogen chloride being preferred. The reaction is carried out according to the procedures outlined by Tanner and Bunce, J. Am. Chem. Soc., 91, 3028 (1969).

[0062] In step c, the appropriate cyclopropyl halocumylketone compound of structure (11) is cyanated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in step a.

[0063] In step d, the appropriate cyclopropyl cumylketone derivative of structure (9) is cyanated to give the corresponding cyclopropyl cyanocumylketone compound of structure (20) as described previously in step b.

[0064] In step e, the appropriate ω-halo-haloethylphenylketone compound of structure (12) is cyanated to give the corresponding ω-halo-cyanoethylphenylketone compound of structure (21) as described previously in step a.

[0065] In step f, the appropriate ω-halo-ethylphenylketone compound of structure (6) is cyanated to give the corresponding ω-halo-cyanoethylphenylketone compound of structure (21) as described previously in step b.

[0066] In step g, the appropriate ω-halo halotolylketone compound of structure (13) is cyanated to give the corresponding ω-halo cyanotolylketone compound of structure (22) as described previously in step a.

[0067] In step h, the appropriate ω-halo tolylketone compound of structure (4) is cyanated to give the corresponding ω-halo cyanotolylketone compound of structure (22) as described previously in step b.

[0068] In step i, the appropriate cyclopropyl ethylphenylketone compound of structure (7) is cyanated to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step b.

[0069] In step j, the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is cyanated to give the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step a.

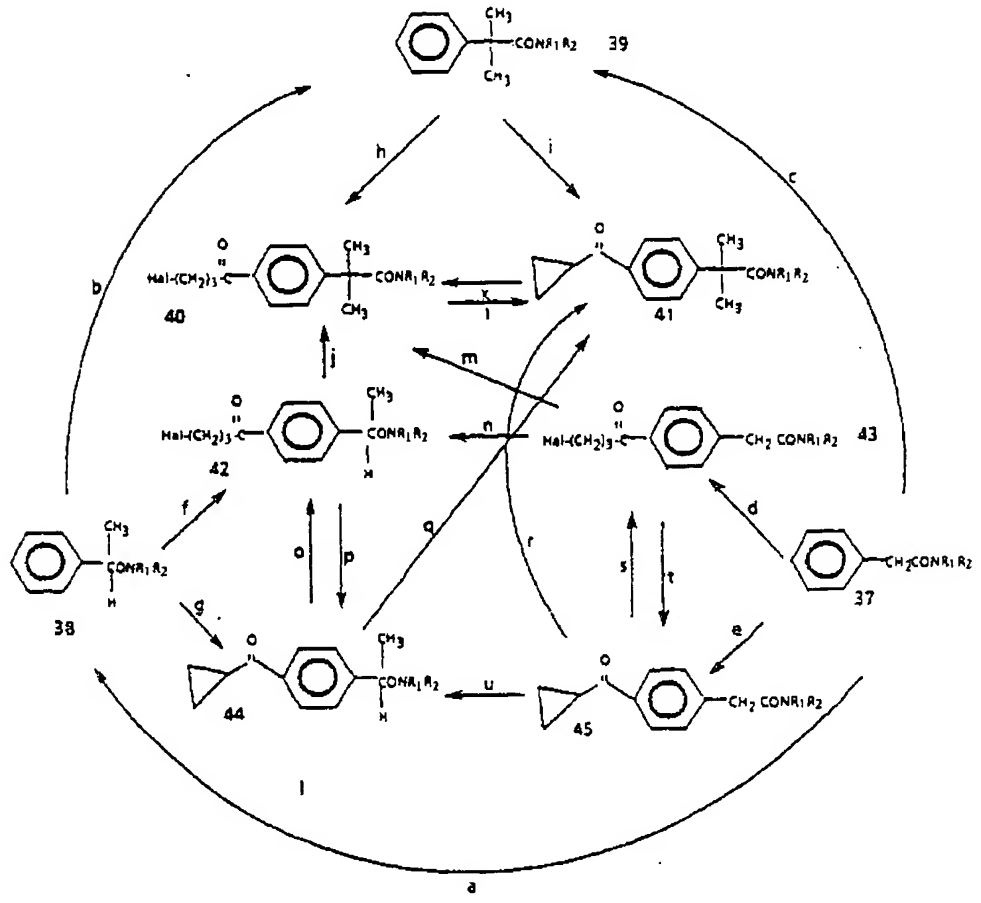
[0070] In step k, the appropriate cyclopropyl tolylketone compound of structure (5) is cyanated to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step b.

[0071] In step l, the appropriate cyclopropyl halotolylketone of structure (15) is cyanated to give the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step a.

[0072] Starting materials for use in Reference-Scheme D are readily available to one of ordinary skill in the art.

[0073] The novel intermediates of formula (III), may be prepared as described in Scheme G. In Scheme G, all substituents are as previously defined unless otherwise indicated.

Scheme G



[0074] Scheme G provides alternative various general synthetic procedures for preparing the novel intermediates

of formula (III).

[0075] In step a, the appropriate phenylacetic acid amide compound of structure (37) is methylated to give the corresponding α-methylphenylacetic acid amide compound of structure (38) as described previously in Scheme A, step a.

[0076] Appropriate phenylacetic acid amide compound of structure (37) are prepared from the corresponding phenylacetic acid by standard amide-forming reactions as are known in the art. The appropriate phenylacetic acids may be prepared by hyrdolysis of the corresponding 2-cyano-2-propylbenzene compound of structure (27) by techniques and procedures well known and appreciated by one of ordinary skill in the art.

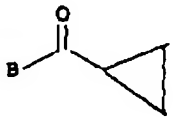
[0077] In step b, the appropriate α-methylphenylacetic acid amide compound of structure (38) is methylated to give the corresponding α,α-dimethylphenylacetic acid amide compound of structure (39) as described previously in Scheme A, step a.

[0078] Appropriate α-methylphenylacetic acid amide compound of structure (38) are prepared from the corresponding α-methylphenylacetic acid by standard amide-forming reactions as are known in the art as as described in step a.

[0079] In step c, the appropriate phenylacetic acid amide compound of structure (37) is dimethylated to give the corresponding α,α-dimethylphenylacetic acid amide compound of structure (39) as described previously in Scheme A, step c.

[0080] In step d, the appropriate phenylacetic acid amide compound of structure (37) is acylated with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) as described previously in Scheme A, step d.

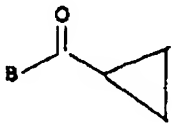
[0081] In step e, the appropriate phenylacetic acid amide compound of structure (37) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropylketo-phenylacetic acid amide compound of structure (45) as described previously in Scheme A, step e.

[0082] In step f, the appropriate α-methylphenylacetic acid amide compound of structure (38) is acylated with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) as described previously in Scheme A, step d.

[0083] In step g, the appropriate α-methylphenylacetic acid amide compound of structure (38) is acylated with an appropriate cyclopropyl compound of the structure

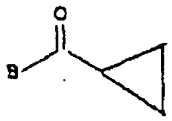


wherein B is as previously defined to give the corresponding cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step e.

[0084] In step h, the appropriate α,α-dimethylphenylacetic acid amide compound of structure (39) is acylated with an appropriate ω-halo compound of the structure Hal-$(CH_2)_n$-C(=O)-B, wherein B is Hal or hydroxy, Hal is Cl, Br or I and n is as previously defined to give the corresponding ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (40) as described previously in Scheme A, step d.

[0085] Appropriate α,α-dimethylphenylacetic acid amide compounds of structure (39) are prepared from the corresponding α,α-dimethylphenylacetic acid by standard amide-forming reactions as are known in the art as as described in step a.

[0086] In step i, the appropriate α,α-dimethylphenylacetic acid amide compound of structure (39) is acylated with an appropriate cyclopropyl compound of the structure



wherein B is as previously defined to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step e.

[0087] In step j, the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) is methylated to give the corresponding ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (40) as described previously in Scheme a, step a.

[0088] In step k, the cyclopropyl functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) is ring-opened to give the corresponding ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (40) wherein n = 3 as described previously in Scheme A, step j.

[0089] In step l, the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid amide compound of structure (40) wherein n = 3 is ring-closed to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step k.

[0090] In step m, the appropriate ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) is dimethylated to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid amide compound of structure (40) as described previously in Scheme A, step c.

[0091] In step n, the appropriate ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) is methylated to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) as described previously in Scheme A, step a.

[0092] In step o, the cyclopropyl functionality of the appropriate cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) is ring-opened to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) wherein n = 3 as described previously in Scheme A, step j.

[0093] In step p, the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) wherein n = 3 is ring-closed to give the corresponding cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step k.

[0094] In step q, the appropriate cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) is methylated to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step a.

[0095] In step r, the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is dimethylated to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step c.

[0096] In step s, the cyclopropyl functionality of the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is ring-opened to give the corresponding ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) wherein n = 3 as described previously in Scheme A, step j.

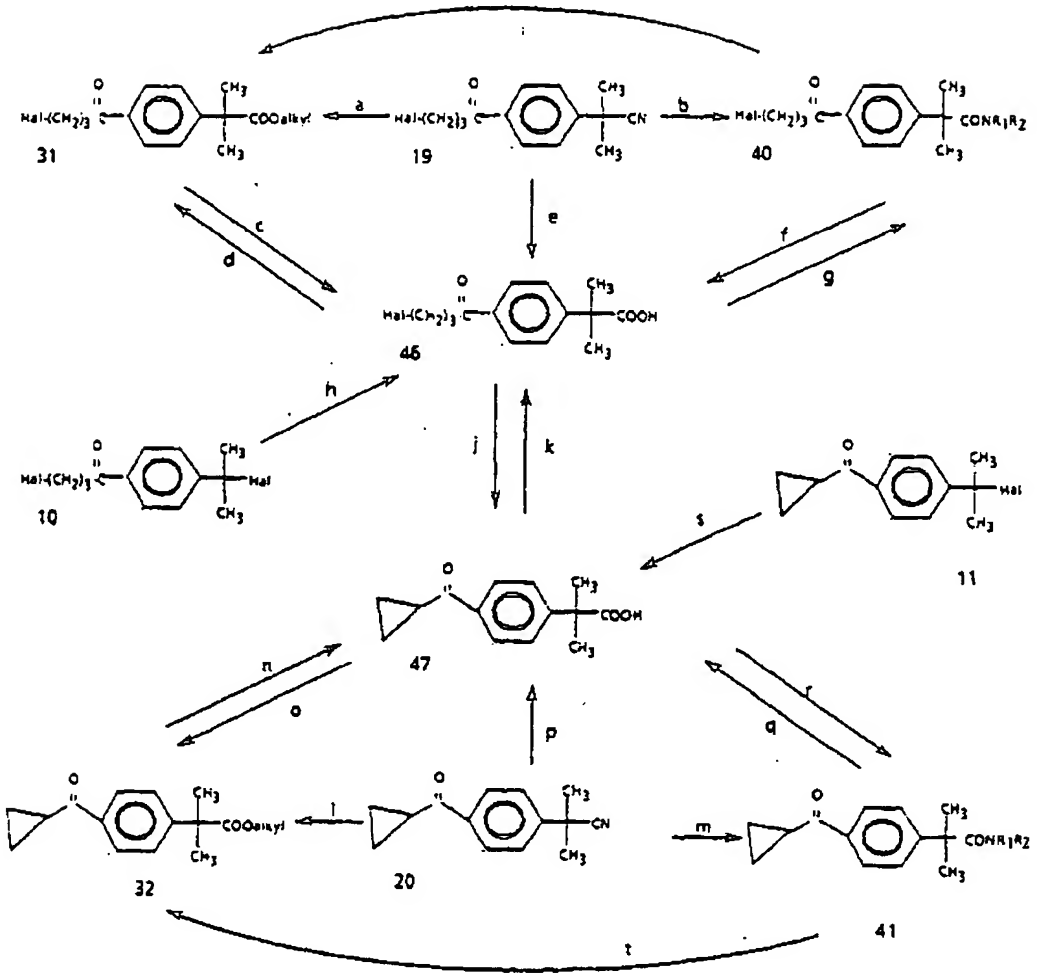
[0097] In step t, the appropriate ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) wherein n = 3 is ring-closed to give the corresponding cyclopropylketo-phenylacetic acid amide compound of structure (45) as described previously in Scheme A, step k.

[0098] In step u, the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is methylated to give the corresponding cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step a.

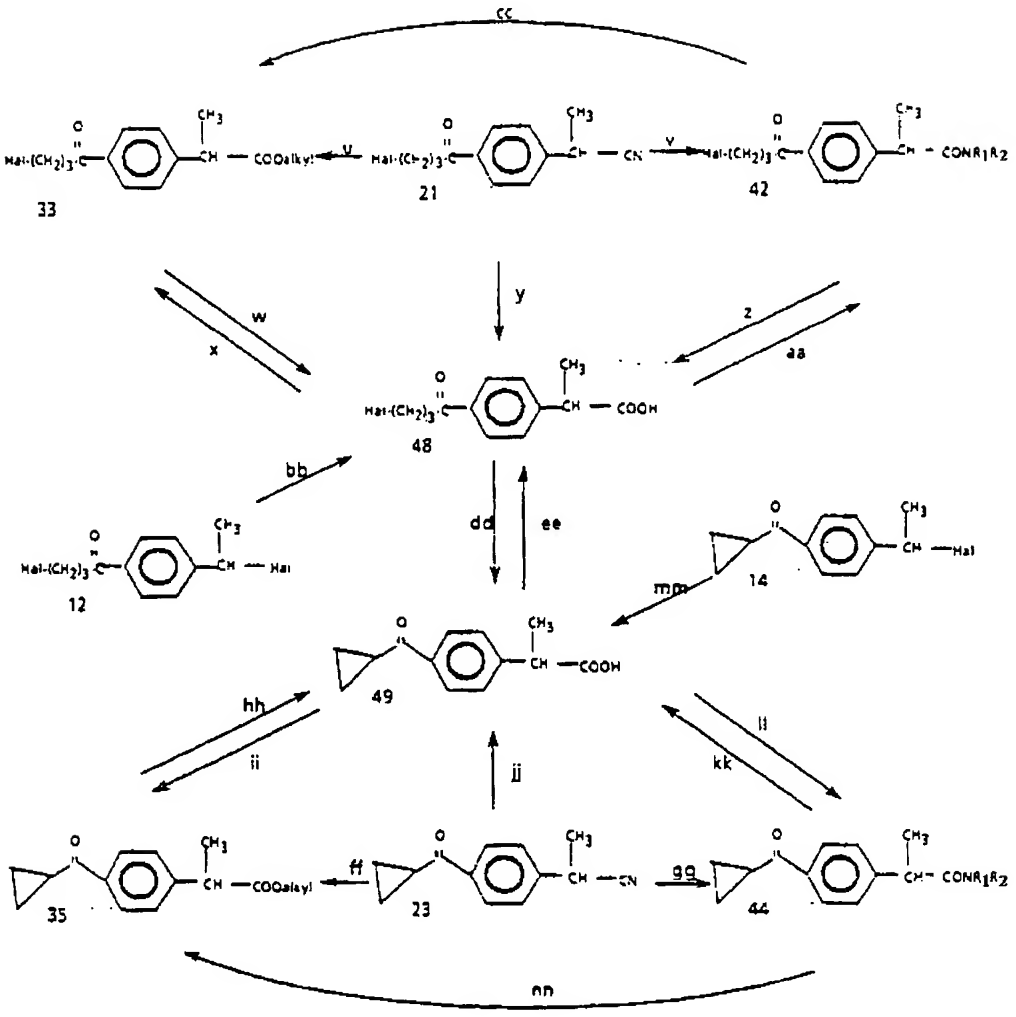
[0099] Starting materials for use in Scheme C are readily available to one of ordinary skill in the art.

[0100] The novel intermediates of formula (III), may be prepared as described in Scheme H. In Scheme H, all substituents are as previously defined unless otherwise indicated.

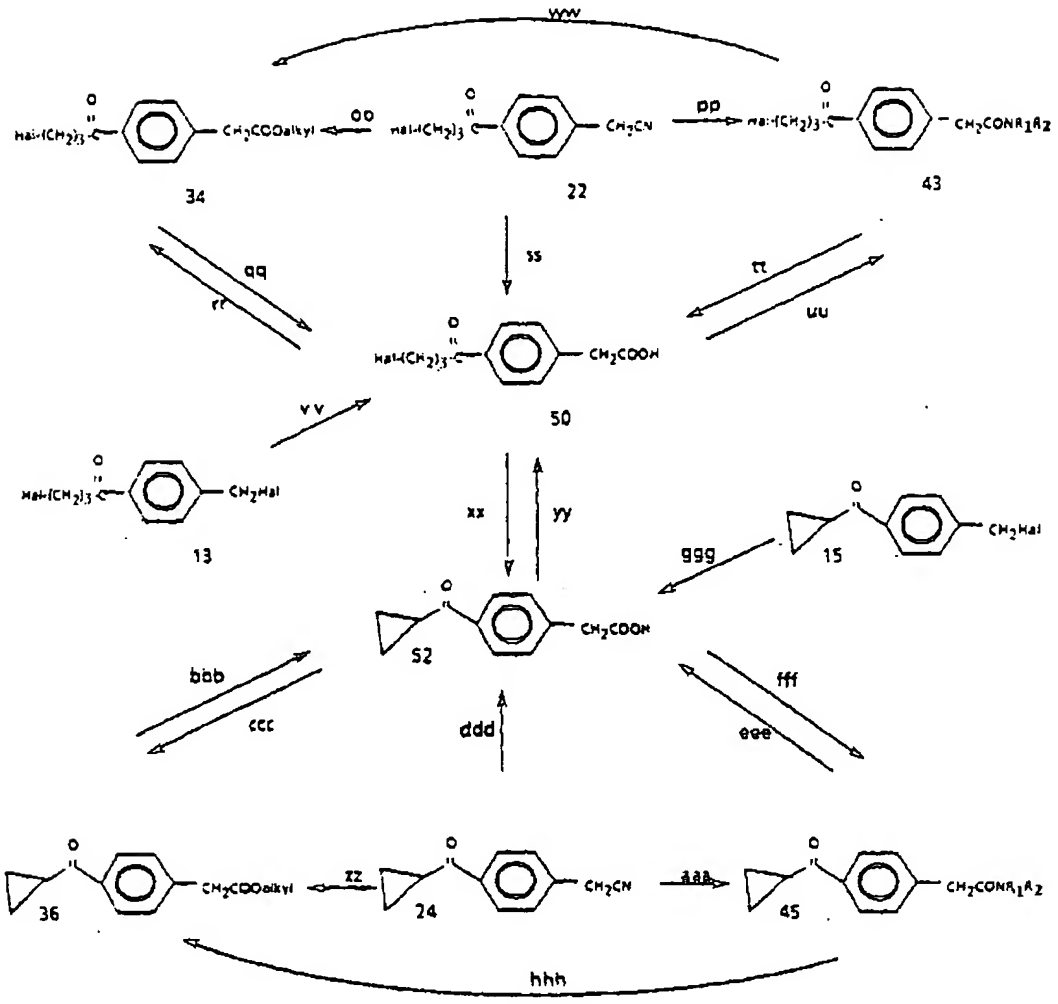
Scheme H


Hal-(CH2)3
COOalkyl
CN
CONR1R2
COOH
Hal
CH3
31
19
40
46
10
11
47
32
20
41
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
r
s
t

Scheme H Cont.



Scheme H Cont.



[0101] Scheme H provides various general synthetic procedures for preparing the above referred novel intermediates of formula (III).

[0102] In step a, the nitrile functionality of the appropriate ω-halo-cyanocumylketone compound of structure (19) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31).

[0103] For example, the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31) may be prepared by reacting an appropriate ω-halo-cyanocumylketone compound of structure (19) with an appropriate C_1-C_6 alcohol in the presence of a suitable anhydrous acid followed by treatment with water. Examples of appropriate alcohols are methanol, ethanol, propanol, and the like, with methanol being preferred. Examples of appropriate acids are hydrogen chloride and hydrogen bromide, with hydrogen chloride being preferred. The reaction time varies from about 1/2 hour to 48 hours, preferably 3 to 5 hours and the reaction temperature varies from about -20°C to room temperature, preferably -10°C to 0°C. The ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (28) is recovered from the reaction zone by evaporation of the solvent followed by extraction as is known in the art. The ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31) may be purified by procedures well known in the art, such as chromatography.

[0104] In step b, the nitrile functionality of the appropriate ω-halo-cyanocumylketone compound of structure (19) is converted to the corresponding amide to give the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid amide compound of

structure (40) wherein R_1 and R_2 are both hydrogen.

[0105] For example, hydrolysis may be achieved by using a suitable acid, such as concentrated hydrochloric acid as is known in the art.

[0106] In step c, the carboxy ester functionality of the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31) is hydrolyzed to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46).

[0107] For example, hydrolysis may be achieved by using a suitable non-nucleophilic base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for ester cleavage include potassium carbonate in methanol, methanolic ammonia, potassium carbonate, potassium hydroxide, calcium hydroxide, sodium hydroxide, magnesium hydroxide, sodium hydroxide/pyridine in methanol, potassium cyanide in ethanol and sodium hydroxide in aqueous alcohols, with potassium hydroxide being preferred. The reaction is typically carried out in an aqueous lower alcohol solvent, such as methanol, ethanol, isopropyl alcohol, n-butanol, 2-ethoxyethanol or ethylene glycol or pyridine, at temperatures ranging from room temperature to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 100 hours.

[0108] In step d, the carboxy functionality of the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31).

[0109] For example, one such method involves reacting an appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) with an excess of an appropriate C_1-C_6 alcohol which is straight or branched in the presence of a small amount of mineral acid, such as hydrochloric acid or sulfuric acid, hydrochloric acid being preferred, at reflux. Another suitable method involves reacting an appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) with an excess of diazomethane in a suitable solvent such as ether at room temperature to give the methyl ester. In addition, the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (28) may also be prepared by reacting an appropriate ω'-halo-α'-keto-α,α-di-methylphenylacetic acid compound of structure (46) with an excess of 2,2-dimethoxypropane in a suitable solvent such as methanol at 0°C to room temperature to give the methyl ester. Another suitable method involves first reacting an appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) with thionyl chloride in a suitable solvent such as methylene chloride to give an intermediate acid chloride, followed by addition of a suitable C_1 to C_6 alcohol which is straight or branched. Another suitable method involves the alkylation of the carboxylate anion with an appropriate electrophile, such as dimethyl sulfate or ethyl bromide, to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31). Such methods are well known in the art and are described in *J. Org. Chem.*, **29**, 2490-2491 (1964).

[0110] Alternatively, step k and step d may be combined and the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (34) wherein n = 3 may be prepared from the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (50).

[0111] Alternatively, step p, step k and step d may be combined and the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31) wherein n = 3 may be prepared from the corresponding cyclopropyl cyanocumylketone compound of structure (20).

[0112] In step e, the nitrile functionality of the appropriate ω-halo-cyanocumylketone compound of structure (19) is converted to the corresponding carboxy to give the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46).

[0113] For example, hydrolysis may be achieved by using a suitable acid, such as concentrated hydrochloric acid as is known in the art.

[0114] In step f, the amide functionality of the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid amide compound of structure (40) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46).

[0115] For example, hydrolysis may be achieved by using a suitable non-nucleophilic base, such as sodium methoxide in methanol as is known in the art. Other methods known in the art for ester cleavage include potassium carbonate in methanol, methanolic ammonia, potassium carbonate, potassium hydroxide, calcium hydroxide, sodium hydroxide, magnesium hydroxide, sodium hydroxide/pyridine in methanol, potassium cyanide in ethanoland sodium hydroxide in aqueous alcohols, with potassium hydroxide being preferred. The reaction is typically carried out in an aqueous lower alcohol solvent, such as methanol, ethanol, isopropyl alcohol, n-butanol, 2-ethoxyethanol or ethylene glycol or pyridine, at temperatures ranging from room temperature to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 100 hours.

[0116] In step g, the carboxy functionality of the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid amide compound of structure (40).

[0117] In step h, the α-halo functionality of the appropriate ω-halo-halocumylketone compound of structure (10) is carboxylated to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46).

[0118] For example, a solution of the appropriate ω-halo-halocumylketone compound of structure (10) and a suitable catalyst, such as tetraethylammonium bromide, in a suitable polar aprotic organic solvent, such as acetonitrile, N,N-dimethylacetamide, 1-methyl-2-pyrrolidinone or dimethylformamide, are placed in a jacketed glass cell and fitted with an expanded silver mesh cathode, magnesium anode and carbon dioxide delivery tube. Rotation of the electrodes provides stirring, while electrical contact with the electrodes is made via spring loaded sliding carbon brushes placed against the concentric metal shafts (insulated from each other with a length of plastic tubing) onto which the electrodes are mounted. Carbon dioxide is introduced into the cell at pressures of 1-10 atm, for a period of time ranging from 30 minutes to 50 hours and at a temperature range of from -30°C to 50°C. The corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) is isolated, after acidification with a suitable mineral acid, such as hydrochloric acid, by extractive methods as are known in the art.

[0119] It is preferred that the ω-halo functionality of the appropriate ω-halo-halocumylketone compound of structure (10) for use in step h be a ω-chloro.

[0120] Alternatively, the treatment of appropriate ω-halo-halocumylketone compound of structure (10) with a transition metal catalyst such as palladium, nickel or cobalt, optionally in the presence of a phosphine catalysis using low to modest pressures of carbon monoxide as described by Stahly et al. in U.S. Patent 4,990,658, 1991 also provides the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46).

[0121] In step i, the appropriate the amide functionality of the appropriate ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (40) is converted to the corresponding ester to give the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31).

[0122] For example,the appropriate ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (40) is reacted with an appropriate hydrogen halide in an appropriate organic solvent such as ethanol. The reaction is typically conducted at a temperature range of from room temperature to reflux and for a period of time ranging from 5 minutes to 1 hour. The ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (31) is recovered from the reaction zone by extractive methods as is known in the art.

[0123] In step j, the appropriate ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) is ring-closed to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) as described previously in Scheme A, step k.

[0124] In step k, the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) is ring-opened to give the corresponding ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) wherein n = 3 as described previously in Scheme A, step j.

[0125] In step l, the nitrite functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the cyclopropylketo-α,α-dimethylphenylacetic acid ester compound of structure (32) as described previously in step a.

[0126] In step m, the nitrile functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding amide to give the ω'-halo-α'-keto-α,α-di-methylphenylacetic acid amide compound of structure (41) wherein R_1 and R_2 are both hydrogen as described previously in step b.

[0127] In step n, the carboxy ester functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid ester compound of structure (32) is hydrolyzed to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) as described previously in step c.

[0128] In step o, the carboxy functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid ester compound of structure (32) as described previously in step d.

[0129] In step p, the nitrile functionality of the appropriate cyclopropyl cyanocumylketone compound of structure (20) is converted to the corresponding carboxy to give the cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) as described previously in step e.

[0130] In step q, the amide functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) as described previously in step f.

[0131] In addition, step q and step k may be combined and the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid compound of structure (46) may be prepared from the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in Scheme A, step j.

[0132] In step r, the carboxy functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) as described previously in step g.

[0133] In step s, the α-halo functionality of the appropriate cyclopropyl halocumylketone compound of structure (11)

is carboxylated to give the corresponding cyclopropylketo-α,α-dimethylphenylacetic acid compound of structure (47) as described previously in step h.

[0134] In step t, the appropriate the amide functionality of the appropriate cyclopropylketo-α,α-dimethylphenylacetic acid amide compound of structure (41) is converted to the corresponding ester to give the cyclopropylketo-α,α-dimethylphenylacetic acid ester compound of structure (32) as described previously in step l.

[0135] In step u, the nitrile functionality of the appropriate ω-halo-cyanoethylphenylketone compound of structure (21) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the ω'-halo-α'-keto-α-methylphenylacetic acid ester compound of structure (33) as described previously in step a.

[0136] In step v, the nitrile functionality of the appropriate ω-halo-cyanoethylphenylketone compound of structure (21) is converted to the corresponding amide to give the ω'-halo-α-keto-α-methylphenylacetic acid amide compound of structure (42) wherein R_1 and R_2 are both hydrogen as described previously in step b.

[0137] In step w, the carboxy ester functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid ester compound of structure (33) is hydrolyzed to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) as described previously in step c.

[0138] In step x, the carboxy functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid ester compound of structure (33) as described previously in step d.

[0139] Alternatively, step ee and step x may be combined and the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (33) may be prepared from the corresponding cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in step d.

[0140] Alternatively, step jj, step ee and step x may be combined and the ω'-halo-α'-keto-α,α-dimethylphenylacetic acid ester compound of structure (33) may be prepared from the corresponding cyclopropyl cyanoethylphenylketone compound of structure (23) as described previously in step d.

[0141] In step y, the nitrile functionality of the appropriate ω-halo-cyanoethylphenylketone compound of structure (21) is converted to the corresponding carboxy to give the ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) as described previously in step e.

[0142] In step z, the amide functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) as described previously in step f.

[0143] In step aa, the carboxy functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) as described previously in step g.

[0144] In step bb, the α-halo functionality of the appropriate ω-halo-haloethylphenylketone compound of structure (12) is carboxylated to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) as described previously in step h.

[0145] In step cc, the appropriate the amide functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) is converted to the corresponding ester to give the ω'-halo-α'-keto-α-methylphenylacetic acid ester compound of structure (33) as described previously in step i.

[0146] In step dd, the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) is ring-closed to give the corresponding cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in Scheme A, step k.

[0147] In step ee, the appropriate cyclopropylketo-α-methylphenylacetic acid compound of structure (49) is ring-opened to give the corresponding ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) as described previously in Scheme A, step j.

[0148] In step ff, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the cyclopropylketo-α-methylphenylacetic acid ester compound of structure (35) as described previously in step a.

[0149] In step gg, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is converted to the corresponding amide to give the cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) wherein R_1 and R_2 are both hydrogen as described previously in step b.

[0150] In step hh, the carboxy ester functionality of the appropriate cyclopropylketo-α-methylphenylacetic acid ester compound of structure (35) is hydrolyzed to give the corresponding cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in step c.

[0151] In step ll, the carboxy functionality of the appropriate cyclopropylketo-α-methylphenylacetic acid compound of structure (49) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-α-methylphenylacetic acid ester compound of structure (35) as

described previously in step d.

[0152] In step jj, the nitrile functionality of the appropriate cyclopropyl cyanoethylphenylketone compound of structure (23) is converted to the corresponding carboxy to give the cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in step e.

[0153] In step kk, the amide functionality of the appropriate cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in step f.

[0154] In addition, step kk and step ee may be combined and the ω'-halo-α'-keto-α-methylphenylacetic acid compound of structure (48) wherein n = 3 may be prepared from the corresponding cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) as described previously in Scheme A, step j.

[0155] In step ll, the carboxy functionality of the appropriate cyclopropylketo-α-methylphenylacetic acid compound of structure (49) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-α-methylphenylacetic acid amide compound of structure (44) as described previously in step g.

[0156] In step mm, the α-halo functionality of the appropriate cyclopropyl haloethylphenylketone compound of structure (14) is carboxylated to give the corresponding cyclopropylketo-α-methylphenylacetic acid compound of structure (49) as described previously in step h.

[0157] In step nn, the appropriate the amide functionality of the appropriate ω'-halo-α'-keto-α-methylphenylacetic acid amide compound of structure (42) is converted to the corresponding ester to give the ω'-halo-α'-keto-α-methylphenylacetic acid ester compound of structure (33) as described previously in step l.

[0158] In step oo, the nitrile functionality of the appropriate ω-halo cyanotolylketone compound of structure (22) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) as described previously in step a.

[0159] In step pp, the nitrile functionality of the appropriate ω-halo cyanotolylketone compound of structure (22) is converted to the corresponding amide to give the ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) wherein R_1 and R_2 are both hydrogen as described previously in step b.

[0160] In step qq, the carboxy ester functionality of the appropriate ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) is hydrolyzed to give the corresponding ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in step c.

[0161] In step rr, the carboxy functionality of the appropriate ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) as described previously in step d.

[0162] Alternatively, step yy and step rr may be combined and the ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) may be prepared from the corresponding ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in step d.

[0163] Alternatively, step ddd, step yy and step rr may be combined the ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) may be prepared from the corresponding cyclopropyl cyanotolylketone compound of structure (24) as described previously in step d.

[0164] In step ss, the nitrile functionality of the appropriate ω-halo cyanotolylketone compound of structure (22) is converted to the corresponding carboxy to give the ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in step e.

[0165] In step tt, the amide functionality of the appropriate ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in step f.

[0166] In step uu, the carboxy functionality of the appropriate ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) as described previously in step g.

[0167] In step vv, the α-halo functionality of the appropriate ω-halo halotolylketone compound of structure (13) is carboxylated to give the corresponding ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in step h.

[0168] In step ww, the appropriate the amide functionality of the appropriate ω'-halo-α'-keto-phenylacetic acid amide compound of structure (43) is converted to the corresponding ester to give the ω'-halo-α'-keto-phenylacetic acid ester compound of structure (34) as described previously in step i.

[0169] In step xx, the appropriate ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) is ring-closed to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in Scheme A, step k.

[0170] In step yy, the appropriate cyclopropylketo-phenylacetic acid compound of structure (51) is ring-opened to give the corresponding ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) as described previously in Scheme A, step j.

[0171] In step zz, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of structure (24) is converted to the corresponding ester by reaction with an appropriate C_1 to C_6 alcohol to give the cyclopropylketo-phenylacetic acid ester compound of structure (36) as described previously in step a.

[0172] In step aaa, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of structure (24) is converted to the corresponding amide to give the cyclopropylketo-phenylacetic acid amide compound of structure (45) wherein R_1 and R_2 are both hydrogen as described previously in step b.

[0173] In step bbb, the carboxy ester functionality of the appropriate cyclopropylketo-phenylacetic acid ester compound of structure (36) is hydrolyzed to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step c.

[0174] In step ccc, the carboxy functionality of the appropriate cyclopropylketo-phenylacetic acid compound of structure (51) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-phenylacetic acid ester compound of structure (36) as described previously in step d.

[0175] In step ddd, the nitrile functionality of the appropriate cyclopropyl cyanotolylketone compound of structure (24) is converted to the corresponding carboxy to give the cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step e.

[0176] In step eee, the amide functionality of the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step f.

[0177] In addition, step yy and step eee may be combined and the ω'-halo-α'-keto-methylphenylacetic acid compound of structure (50) may be prepared from the corresponding cyclopropylketo-phenylacetic acid amide compound of structure (45) as described previously in Scheme A, step j.

[0178] In step fff, the carboxy functionality of the appropriate cyclopropylketo-phenylacetic acid compound of structure (51) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding cyclopropylketo-phenylacetic acid amide compound of structure (45) as described previously in step g.

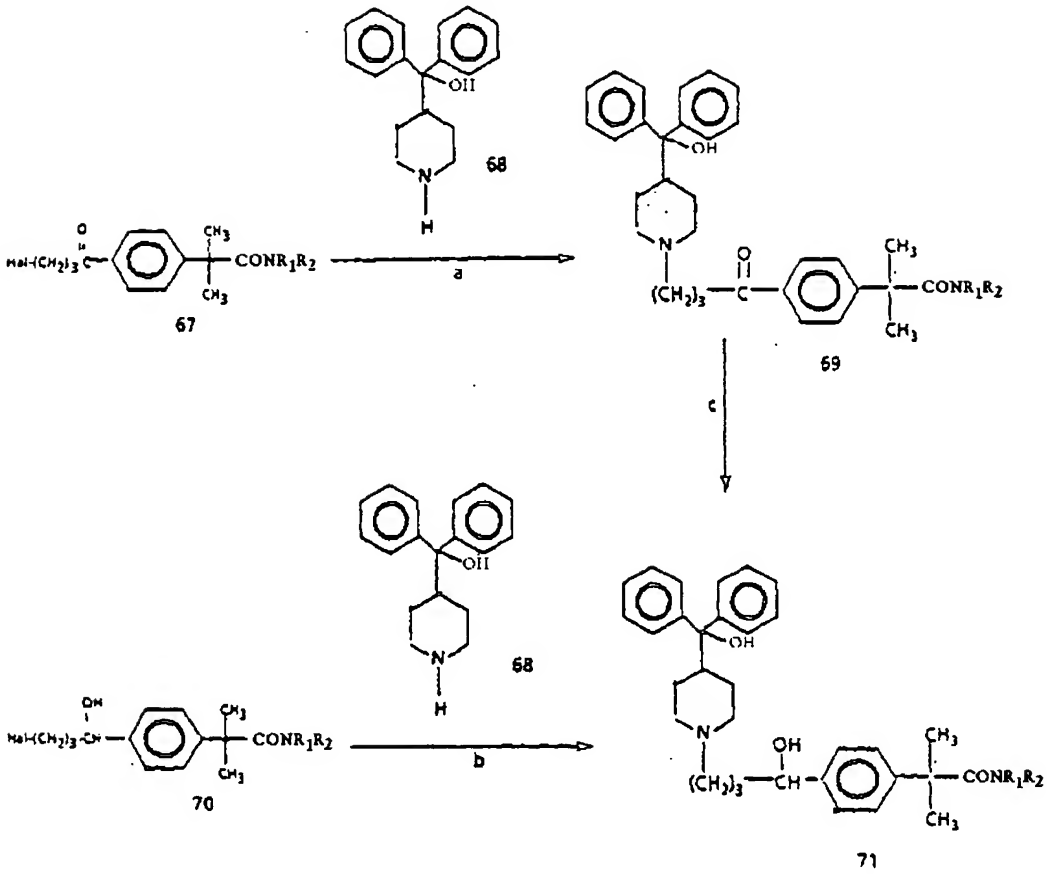
[0179] In step ggg, the α-halo functionality of the appropriate cyclopropyl halotolylketone of structure (15) is carboxylated to give the corresponding cyclopropylketo-phenylacetic acid compound of structure (51) as described previously in step h.

[0180] In step hhh, the appropriate the amide functionality of the appropriate cyclopropylketo-phenylacetic acid amide compound of structure (45) is converted to the corresponding ester to give the cyclopropylketo-phenylacetic acid ester compound of structure (36) as described previously in step i.

[0181] Starting materials for use in Scheme H are readily available to one of ordinary skill in the art.

[0182] The novel intermediates of formula (XI) may be prepared as described in Scheme L. In Scheme L, all substituents are as previously defined unless otherwise indicated.

Scheme L



[0183] Scheme L provides various general synthetic procedures for preparing the novel intermediates of formula (XI).

[0184] In step a, the ω'-halo functionality of the appropriate ω'-halo-α'-keto-α,α-dimethylphenyl compound of structure (67) is alkylated with the appropriate piperidine compound of structure (68) to give the corresponding ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69).

[0185] For example, the ω'-piperidine- α'-keto-α,α-dimethylphenyl compound of structure (69) may be prepared by reacting the appropriate ω'-halo-α'-keto-α,α-dimethylphenyl compound of structure (67) with the appropriate piperidine compound of structure (68) in a suitable solvent preferably in the present of a suitable non-nucleophilic base and optionally in the presence of a catalytic amount of an iodide source, such as potassium or sodium iodide. The reaction time varies from about 4 to 120 hours and the reaction temperature varies from about 70°C to the reflux temperature of the solvent. Suitable solvent for the alkylation reaction include alcohol solvents such as, methanol, ethanol, isopropyl alcohol, or n-butanol; ketone solvents, such as, cyclohexanone, methyl isobutyl ketone; hydrocarbon solvents, such as, benzene, toluene or xylene; halogenated hydrocarbons, such as, chlorobenzene or methylene chloride or dimethylformamide. Suitable non-nucleophilic bases for the alkylation reaction include inorganic bases, for example, sodium bicarbonate, potassium carbonate, or potassium bicarbonate or organic bases, such as, a trialkylamine, for example, triethylamine or pyridine, or an excess of an appropriate piperidine compound of structure (68) may be used.

[0186] For those piperidine compounds of structure (68), it is preferred that OH be unprotected for utilization in the

alkyation reaction of step a, but those hydroxy functionalities present in the piperidine compounds of structure (68), may be protected with a suitable protecting group. The selection and utilization of suitable protecting groups for the piperidine compounds of structure (68), is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for those hydroxy functionalities present include ethers such as tetrahydrothiopyranyl, tetrahydrothiofuranyl, 2-(phenylselenyl) ethyl ether, o-nitrobenzyl ether, trimethylsilyl ether, isopropyldimethylsilyl ether, t-butyldimethylsilyl ether, t-butyldiphenylsilyl ether, tribenzylsilyl ether, triisopropylsilyl ether; and esters, such as acetate ester, isobutyrate ester, pivaloate ester, adamantoate ester, benzoate ester, 2,4,6-trimethylbenzoate (mesitoate) ester, methyl carbonate, p-nitrophenyl carbonate, p-nitrobenzyl carbonate, S-benzyl thiocarbonate and N-phenylcarbamate.

[0187] The piperidine compounds of structure (68) are readily available to one of ordinary skill in the art and are described in US-A- 4,254,129 (March 3, 1981), US-A- 4,254,130 (March 3, 1981), US-A- 4,285,958 (April 25, 1981) and US-A-4,550,116 (Oct. 29, 1985).

[0188] In step b, the ω'-halo functionality of the appropriate ω-halo-α'-hydroxy-α,α-dimethylphenyl compound of structure (70) wherein R_5 is $CONR_6R_7$ is alkylated with the appropriate piperidine compound of structure (68) to give the corresponding ω'-piperidine- α'-hydroxy-α,α-dimethylphenyl compound of structure (71) wherein R_5 is, $CONR_6R_7$ as described previously in step a.

[0189] In step c, the ketone functionality of the appropriate ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 $CONR_6R_7$ is reduced to give the corresponding ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compound of structure (71) wherein R_5 is $CONR_6R_7$.

[0190] For example, reduction of the appropriate ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is, $CONR_6R_7$, using, for example, a suitable reducing agent such as sodium borohydride, potassium borohydride, sodium cyanoborohydride, or tetramethylammonium borohydride is carried out in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours. Other suitable reducing agents are, for example, lithium tri-tert-butylaluminohydride and diisobutylaluminum hydride. These reduction reactions are carried out in suitable solvents diethyl ether, tetrahydrofuran or dioxane at temperatures ranging from about 0°C to the reflux temperature of the solvent, and the reaction time varies from about 1/2 hour to 8 hours.

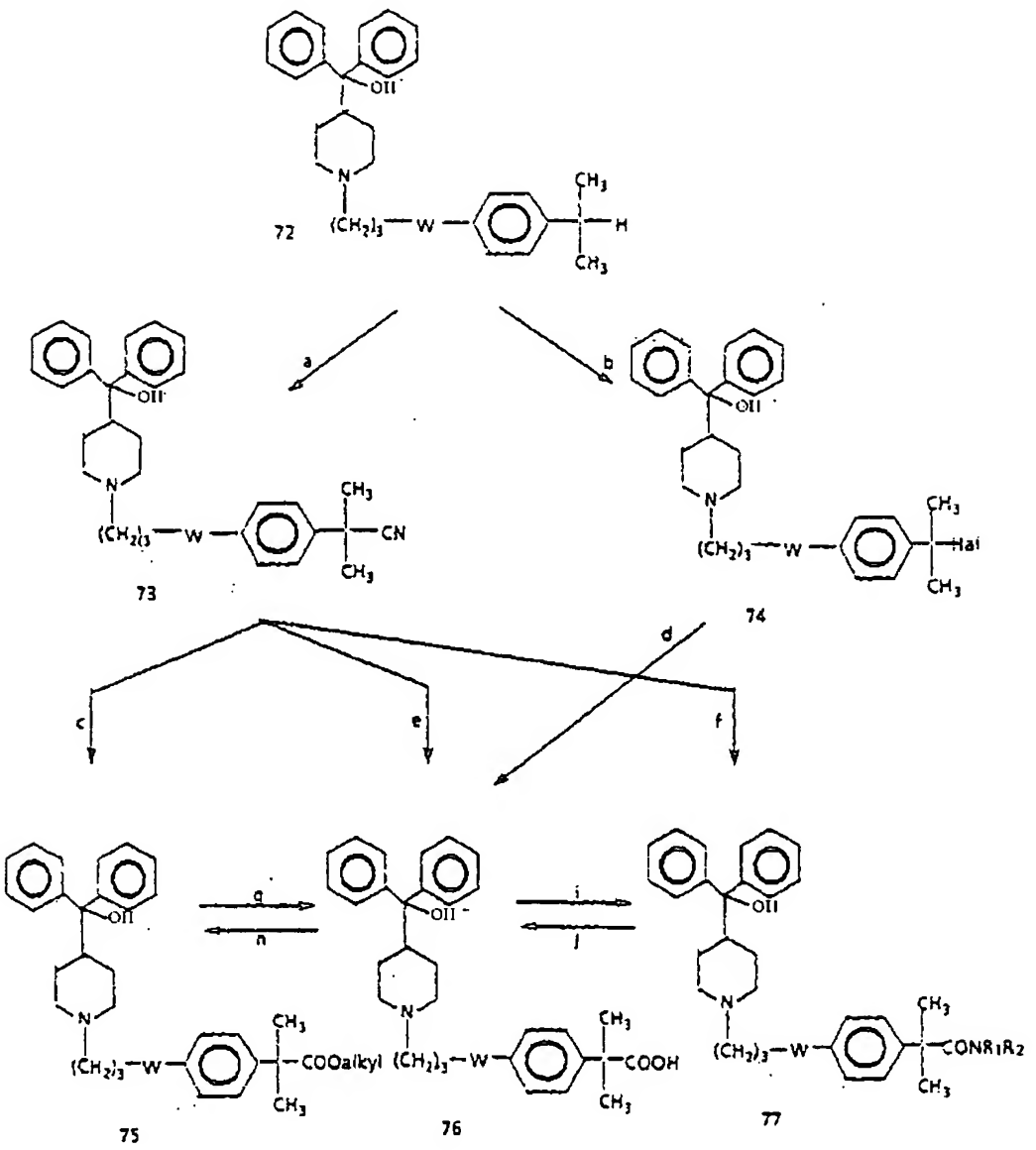
[0191] Catalytic reduction may also be employed in the preparation of appropriate ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compound of structure (71) wherein R_5 is $CONR_6R_7$ from an appropriate ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is, or $CONR_6R_7$, using hydrogen gas in the presence of a suitable catalyst such as Raney nickel, palladium, platinum or rhodium catalysts in lower alcohol solvents, such as, methanol, ethanol, isopropyl alcohol or n-butanol or acetic acid or their aqueous mixtures, or by the use of aluminum isopropoxide in isopropyl alcohol.

[0192] Reduction using sodium borohydride or potassium borohydride is preferred over catalytic reduction for those ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is $CONR_6R_7$ and wherein R_1 and R_2 taken together form a second bond between the carbon atoms bearing R_1 and R_2.

[0193] In addition, a chiral reduction of the appropriate ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is, $CONR_6R_7$, using, for example, (+)-B-chlorodiisopinocamphenylborane gives the corresponding (R)-ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is hydrogen, CN, COOalkyl or $CONR_6R_7$ and (-)-B-chlorodiisopinocamphenylborane gives the corresponding (S)-ω'-piperidine-α'-keto-α,α-dimethylphenyl compound of structure (69) wherein R_5 is, $CONR_6R_7$. Other suitable chiral reducing agents are, (R) and (S)-oxazaborolidine/BH_3, potassium 9-O-(1,2:5,6-di-O-isopropylidine-α-D-glucofuransoyl)-9-boratabicyclo[3.3.1]nonane, (R) and (S)-B-3-pinanyl-9-borabicyclo[3.3.1]nonane, NB-Enantride, Lithium (R)-(+) and (S)-(-)-2,2'-dihydroxy-1,1'-binaphthyl alkoxyl aluminum hydride, (R)-(+) and (S)-(-)-2,2'-dihydroxy-6,6'-dimethylbiphenyl borane-amine complex, tris[[(1S,2S,5R)-2-isopropyl-5-methyl-cyclohex-1-yl]methyl]aluminum, [[(1R,3R)-2,2-dimethylbicyclo[2.2.1]hept-3-yl] methyl]beryllium chloride, (R)-BINAP-ruthenium complex/H_2 and 6,6'-bis(diphenylphosphino)-3,3'-dimethoxy-2,2',4,4'-tetramethyl-1,1'-biphenyl.

[0194] Starting materials for use in Scheme L are readily available to one of ordinary skill in the art.

Scheme M



W = -C(=O)- or -CH(OH)-

[0195] Scheme M provides various alternative general synthetic procedures for preparing the novel intermediates of formula (XI).

[0196] In step a, the appropriate ω'-piperidine-2-methylethylphenyl compound of structure (72) is cyanated to give the corresponding ω'-piperidine-α,α-dimethylphenylacetonitrile compound of structure (73) as described previously in Reference-Scheme D, step b.

[0197] In step b, the appropriate ω'-piperidine-2-methylethylphenyl compound of structure (72) is halogenated to give the corresponding ω'-piperidine-α,α-dimethylbenzyl halide compound of structure (74) as described previously in

Reference-Scheme B, step a.

[0198] In step c, the nitrile functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetonitrile compound of structure (73) is converted to the corresponding ester to give the ω'-piperidine-α,α-dimethylphenylacetic acid ester compound of structure (75) as described previously in Scheme H, step a.

[0199] In step d, the halo functionality of the appropriate ω'-piperidine-α,α-dimethylbenzyl halide compound of structure (74) is converted to the corresponding carboxy to give the ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step h.

[0200] In step e, the nitrile functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetonitrile compound of structure (73) is converted to the corresponding carboxy to give the ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step e.

[0201] In step f, the nitrile functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetonitrile compound of structure (73) is converted to the corresponding amide to give the ω'-piperidine-α,α-dimethylphenylacetic acid amide compound of structure (77) wherein R_1 and R_2 are each hydrogen as described previously in Scheme H, step b.

[0202] In step g, the carboxy ester functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetic acid ester compound of structure (75) is hydrolyzed to give the corresponding ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step c.

[0203] In step h, the carboxy functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) may be esterified by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-piperidine-α,α-dimethylphenylacetic acid ester compound of structure (75) as described previously in Scheme H, step d.

[0204] In step i, the carboxy functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) may be amidated by techniques and procedures well known and appreciated by one of ordinary skill in the art to give the corresponding ω'-piperidine-α,α-dimethylphenylacetic acid amide compound of structure (77) as described previously in Scheme H, step g.

[0205] In step j, the amide functionality of the appropriate ω'-piperidine-α,α-dimethylphenylacetic acid amide compound of structure (77) is converted to the corresponding acid by acid hydrolysis as is known in the art to give the ω'-piperidine-α,α-dimethylphenylacetic acid compound of structure (76) as described previously in Scheme H, step f.

[0206] Starting materials for use in Scheme M are readily available to one of ordinary skill in the art.

[0207] As one skilled in the art would appreciate, the compounds depicted in Schemes A through M which bear α-ketone functionalities may be protected prior to use in the synthesis depicted in Schemes A through M using suitable protecting groups. The selection and utilization of suitable protecting groups for ketone groups is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). For example, suitable protecting groups for ketone functionalities include acyclic acetals and ketals such as dimethyl acetal, cyclic acetals and ketals such as 1,3-dioxanes and 1,3-dioxolanes, dithio acetals and ketals such as 1,3-dithiane and 1,3-dithiolane, hemithio acetals and ketals, O-substituted cyanohydrins, substituted hydrozones, imines, oxazolidines, imidazolidines and thiazolidines.

[0208] As one skilled in the art would appreciate, the compounds depicted in Schemes A through M which bear protected hydroxy and/or ketone functionalities may be reacting with appropriate deprotecting agents prior to use in any of the steps depicted in Schemes A through M. The selection and utilization of appropriate deprotecting reagents is well known by one of ordinary skill in the art and is described in "Protective Groups in Organic Syntheses", Theodora W. Greene, Wiley (1981). Examples of appropriate deprotecting reagents are mineral acids, strong organic acids, Lewis acids, aqueous mineral bases, catalytic hydrogenation and the like.

[0209] For example, cleavage of β-methoxyethoxymethyl (MEM) protecting groups on any of the compounds depicted in Schemes A through M which bear protected hydroxy ketone functionalities, for example, can be achieved by using trifluoroacetic acid at room temperature or using 5 to 8 equivalents of powdered anhydrous zinc bromide in methylene chloride at about 25°C by the general procedure of E. J. Corey et al., *Tetrahedron Letters*, 11, 809-812 **1976**.

[0210] In addition, the individual (R) and (S) isomers of the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) can be prepared by techniques are procedures well known and appreciated by one of ordinary skill in the art.

[0211] For example, the mixture of (R) and (S) isomers of the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) may be subjected to chiral chromatography to give the corresponding individual (R)-ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) and (S)-ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71).

[0212] In addition, the individual (R) and (S) isomers of the ω-halo-α'-hydroxy-α,α-dimethylphenyl compound of structure (70) and the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) can be prepared by techniques and procedures well known and appreciated by one of ordinary skill in the art and described in "Enanatiomers, Racemates, and Resolutions", Jacques, Collet and Wilen, Wiley (1981).

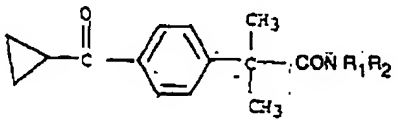
[0213] One such method involves reacting the mixture of (R) and (S) isomers of the ω'-piperidine-α'-hydroxy-α,α-

dimethylphenyl compounds of structure (71) with appropriate chiral acids to give the corresponding mixture of diastereomeric acid addition salts. The individual (R)-ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl chiral acid addition salt compounds of structure (71) and (S)-ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl chiral acid addition salt compounds of structure (71) are obtained by recrystallization and the individual ω'-piperidine-(R)-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) and ω'-piperidine-(S)-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) are obtained by subjecting the individual ω'-piperidine-(R)-α'-hydroxy-α,α-dimethylphenyl chiral acid addition salt compounds of structure (71) and ω'-piperidine-(S)-α'-hydroxy-α,α-dimethylphenyl chiral acid addition salt compounds of structure (71) to base in order to free the piperidine nitrogen from the acid addition complex. Examples of suitable chiral acids are tartaric acid (+), (-), O,O'-dibenzoyltartaric acid (+), (-), O,O'-di-p-toluyltartaric acid (+), (-), 2-Nitrotartranilic acid (+), (-), mandelic acid (+), (-), malic acid (+), (-), 2-phenoxypropionic acid (+), hydratropic acid (+), (-), N-acetylleucine (-), (+), N-(α-methylbenzyl)succinamide (+), (-), N-(α-methylbenzyl)phthalamic acid (+), (-), camphor-10-sulfonic acid (+), 3-bromocamphor-9-sulfonic acid (+), (-), camphor-3-sulfonic acid (+), quinic acid (+), (-), Di-O-isopropylidene-2-oxo-L-gulonic acid (-), Lasalocid (-), 1,1'-binaphthyl-2,2'-phosphoric acid (+), (-), chloestenonesulfonic acid.

[0214] In addition, the individual (R) and (S) isomers of the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) can be prepared by reacting the mixture of (R) and (S) isomers of the ω'-piperidine-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) with appropriate organic chiral acids to give the corresponding mixture of diastereomeric acid esters. The individual ω'-piperidine-(R)-α'-ester-α,α-dimethylphenyl compounds of structure (71) and ω'-piperidine-(S)-α'-ester-α,α-dimethylphenyl compounds of structure (71) are obtained by recrystallization or chromatography and the individual ω'-piperidine-(R)-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) and ω'-piperidine-(S)-α'-hydroxy-α,α-dimethylphenyl compounds of structure (71) are obtained by subjecting the individual ω'-piperidine-(R)-α'-ester-α,α-dimethylphenyl compounds of structure (71) and ω'-piperidine-(S)-α'-ester-α,α-dimethylphenyl compounds of structure (71) to hydrolysis conditions.

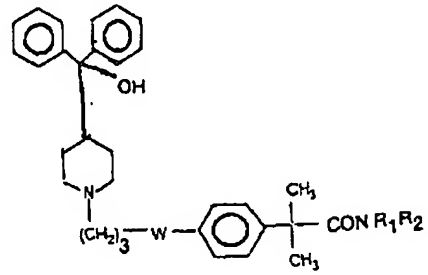
Claims

1. A compound of the formula



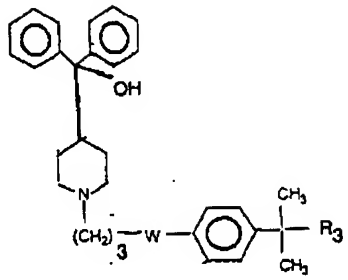
wherein R_1 represents C_1-C_6 alkyl and R_2 represents H, C_1-C_6alkyl, C_1-C_6alkoxy or R_1 and R_2 taken together with the nitrogen atom form a pyrrolidine, piperidine or morpholine ring.

2. A compound of the formula:



wherein W represents -C(=O) - or -CH(OH)-; and the remaining substituents are as defined in claim 1; and pharmaceutical acceptable salts and individual optical isomers thereof.

3. Use of the compound as defined in claim 1, for preparing a compound of the formula I

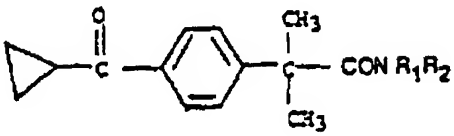


(I)

wherein R_3 is -COOH or -COOalkyl wherein the alkyl moiety has from 1 to 6 carbon atoms and is straight or branched, and wherein W is as defined in claim 2.

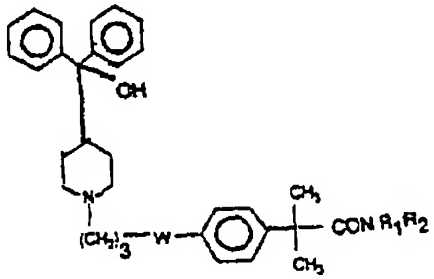
Patentansprüche

1. Verbindung der Formel



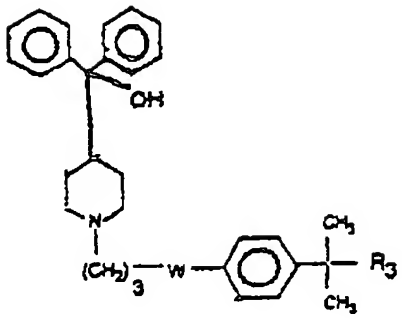
wobei R_1 C_1-C_6-Alkylgruppe und R_2 ein H-Atom, eine C_1-C_6-Alkylgruppe, eine C_1-C_6-Akoxygruppe ist oder R_1 und R_2 zusammengenommen mit dem Stickstoffatom einen Pyrrolidin-, Piperidin- oder Morpholinring bilden.

2. Verbindung der Formel



wobei W —C(=O)- oder —CH(OH)- ist; und die restlichen Substituenten wie in Anspruch 1 definiert sind; und pharmazeutisch verträgliche Salze und die einzelnen optischen Isomere hiervon.

3. Verwendung der Verbindung nach Anspruch 1 zur Herstellung einer Verbindung der Formel I

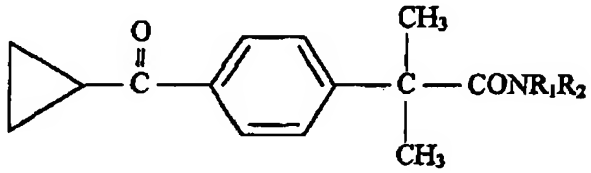


(I)

wobei R_3—COOH oder —COOAlkyl ist, wobei die Alkylgruppe 1 bis 6 Kohlenstoffatome aufweist und geradkettig oder verzweigt ist und wobei W wie in Anspruch 2 definiert ist.

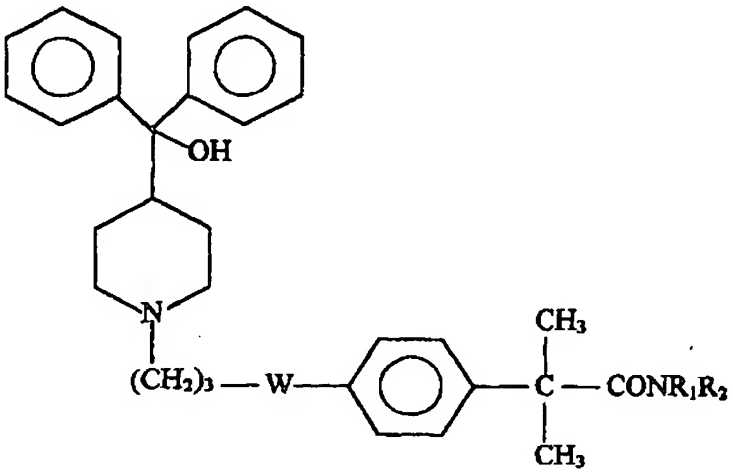
Revendications

1. Composé de formule



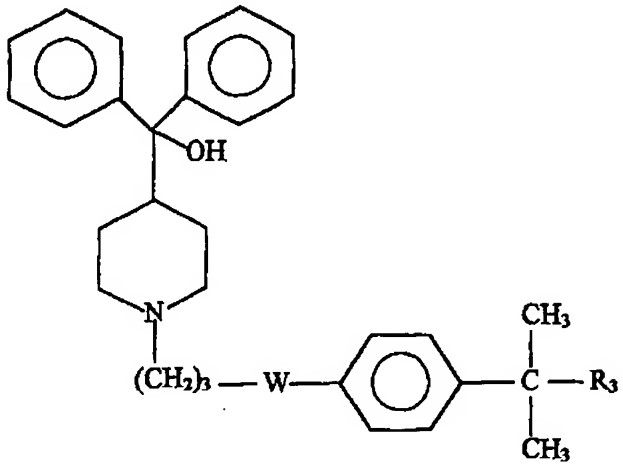
dans laquelle R_1 représente un alkyle en C_1-C_6 et R_2 représente H, un alkyle en C_1-C_6, un alcoxy en C_1-C_6 ou R_1 et R_2 pris ensemble avec l'atome d'azote forment un cycle pyrrolidine, pipéridine ou morpholine.

2. Composé de formule :



dans laquelle W représente -C(=O)- ou -CH(OH)- ; et les substituants restants sont tels que définis dans la revendication 1 ; et sels acceptables pharmaceutiques et isomères optiques individuels de celui-ci.

3. Utilisation du composé tel que défini dans la revendication 1, pour préparer un composé de formule I



(I)

dans laquelle R_3 est -COOH ou -COOalkyl dans lequel l'entité alkyle a entre 1 et 6 atomes de carbone et est linéaire ou ramifiée, et dans laquelle W est tel que défini dans la revendication 2.